Current Issues in Drug Regulation at FDA

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Text from Trade Press Report: Biocentury 10/30/2004

- "Gunning for FDA"
  - Some members of Congress are accusing FDA of a coverup, and collusion with drug companies, over data on an increased risk of suicidality among kids who take antidepressants. Members of Congress also are charging that FDA colluded with Merck to suppress warning about Vioxx's cardiotoxicity. Finally, Congress is investigating the Chiron flu vaccine debacle. All in less than six weeks."

Drug Regulation Policy Environment Has Become More Contentious

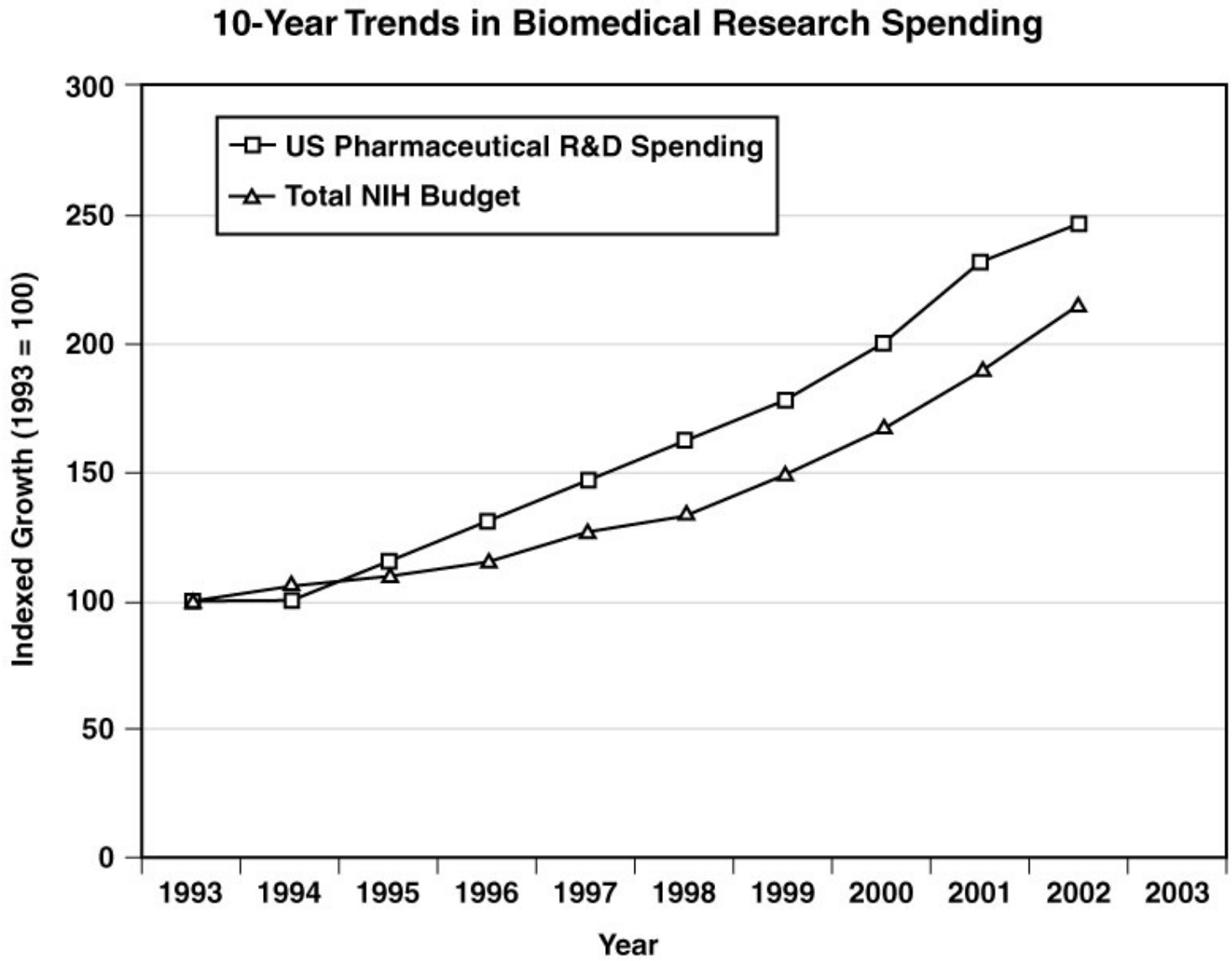
- Product Innovation - Truly New Medicines
- Pricing/Access Issues
- Importation
- Safety of Drug Supply – What's next?
- Clinical Trial Data – Who owns information?
- Product Promotion

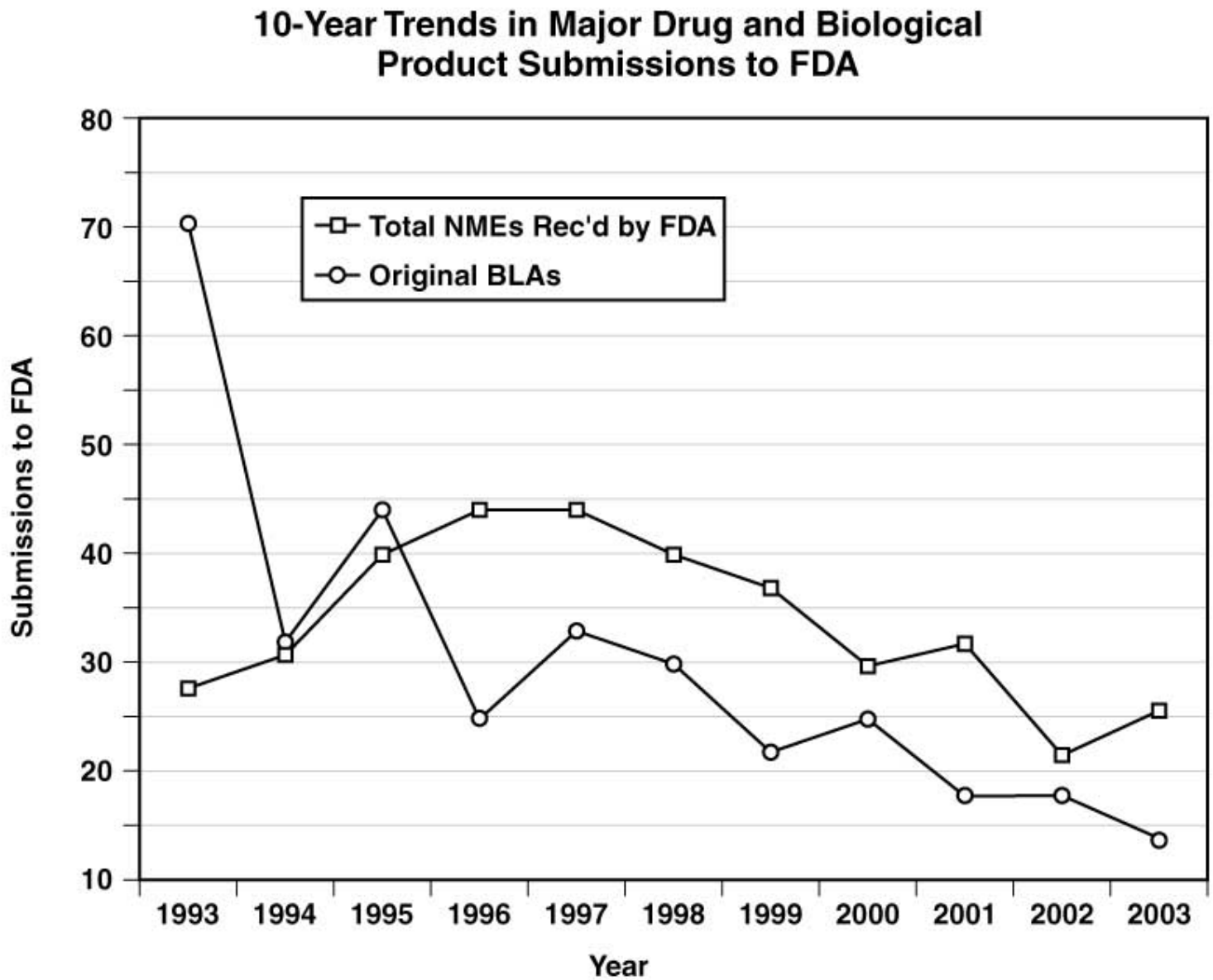
Outline

- Productivity Gap in Medical Product Development
- Diagnosis & FDA role in addressing innovation problem
- Drug Safety Controversy – SSRIs as example & current safety practices & policy issues
- Q & A

Reasons for Optimism About Drug Development

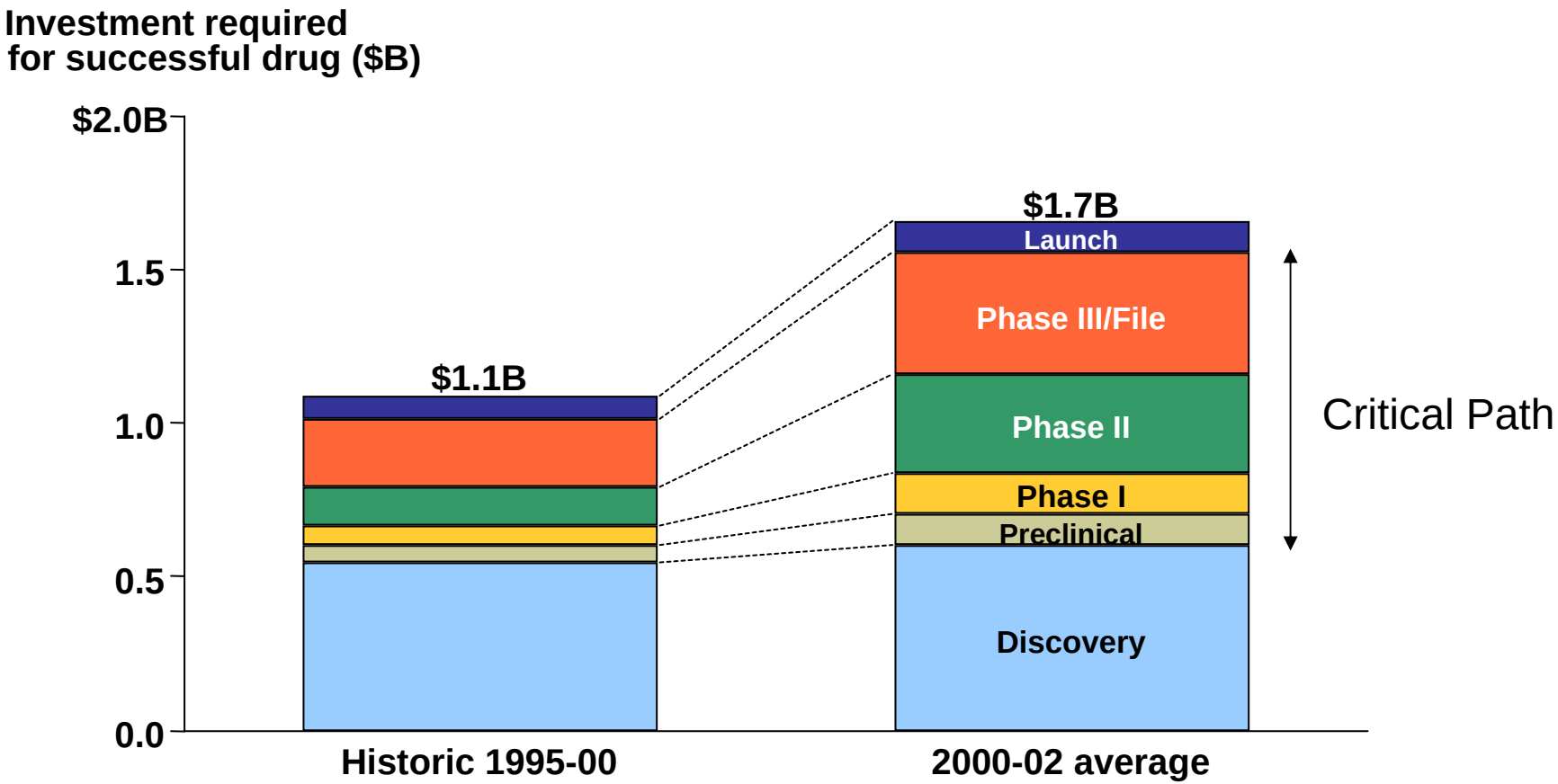
- Sequencing of the human genome
- Genomic and proteomic technologies
- Systems biology
- Advances in medical imaging
- Nanotechnology advances
- Tissue engineering
- Drug discovery: combinatorial chemistry and automated microscale screening


10-Year Trends in Biomedical Research Spending
US Pharmaceutical R&D Spending
Total NIH Budget
Indexed Growth (1993 = 100)
300
250
200
150
100
50
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Year


10-Year Trends in Major Drug and Biological Product Submissions to FDA
Total NMEs Rec'd by FDA
Original BLAs
Submissions to FDA
80
70
60
50
40
30
20
10
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Year

The Costs of Discovering and Developing a New Drug are Increasing Faster Than Our Research Budgets

Change in Average Cost to Develop Successful Drugs Over Time



Source: Bain drug economics model, 2003

The New Drug Pipeline

- Cause is multifactural
- There is clearly a dip or plateau in the new drugs pipeline
  - Genomics & other new science not at full potential (10-15 yrs)
  - Mergers and other business arrangements have decreased candidates
  - Easy targets taken/chronic disease harder to study
  - Failure rate has not improved
  - Rapidly escalating costs & complexity decrease willingness/ability to bring many candidates forward into the clinic

So What?
The Societal Challenge

- Urgency of need for medical product innovation
  - Aging of population
  - Mounting burden of illness
- Reimbursement decisions -- need higher degree of certainty related to performance
- Perception that our investment in basic biomedical research is not delivering on its promise

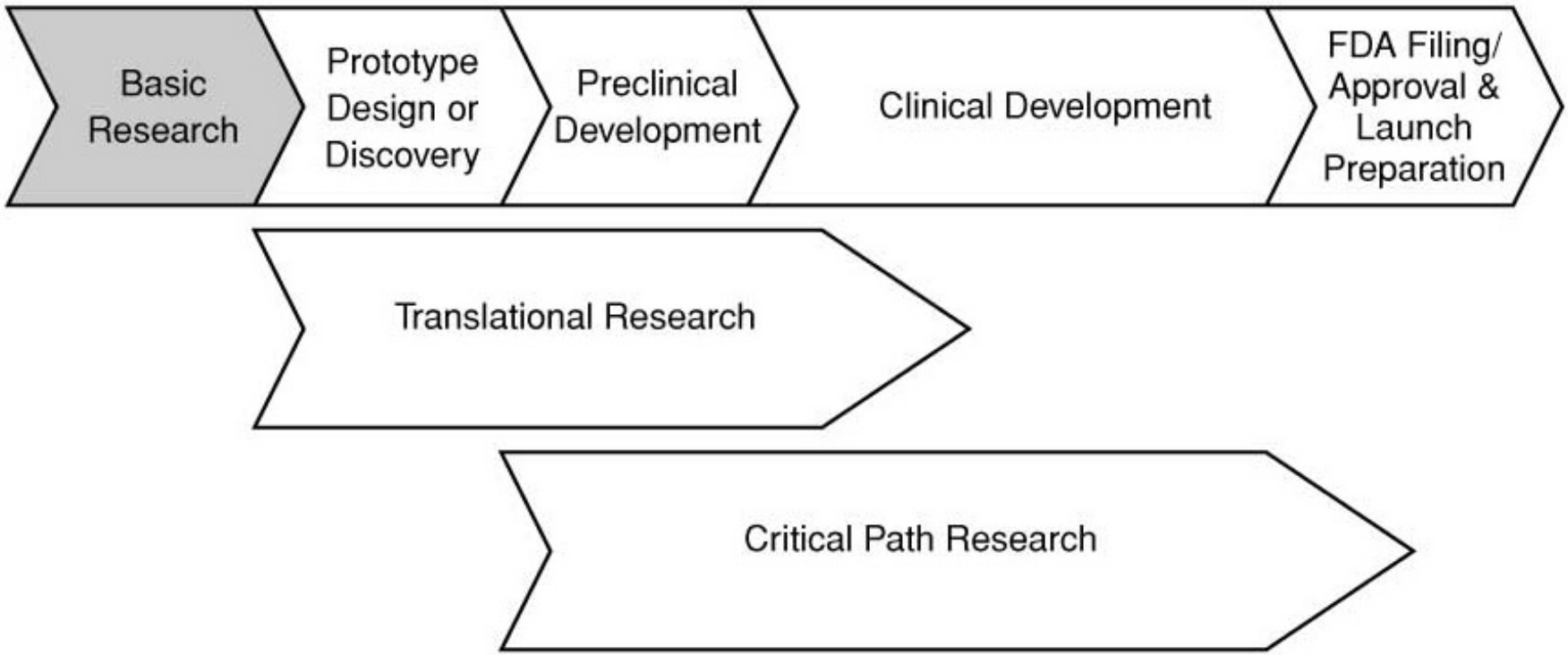
Problem: Development process itself is becoming a serious bottleneck

- Current applied science and infrastructure date from last century
  - Funding and progress in Development science has not kept pace with basic biomedical science.
- Science to evaluate safety and efficacy of potential new medical products, and enable manufacture, is *different* from basic discovery science.
- Need to fill gap in applied science-- to increase productivity and efficiency -- to reduce cost of development process.
- The development process – the “critical path” is becoming a serious bottleneck to delivery of new products

FDA's Critical Path Initiative

Agency's first serious attempt to bring attention and focus to the need for targeted scientific efforts to modernize the techniques and methods used to evaluate the safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture.

Science Underlying The Critical Path of Drug Development



Science to evaluate safety & efficacy of new products, and enable manufacture, is different from basic discovery science

What is on "Critical Path" to Medical Product Development?

Applied science to address 3 key dimensions:

- Assessment of Safety – how to predict if a potential product will be harmful?
- Proof of Efficacy -- how to determine if a potential product will have medical benefit?
- Industrialization – how to manufacture a product at commercial scale with consistently high quality?

FDA Next Steps

- Announce “Critical Path Challenges” list this year
- FDA will be able to lead a number of projects – limited by available funding
- Identification of projects “left behind” should spur additional efforts

- **Scientific Consortia Among Academia, Industry and Government will be needed to accomplish these Goals.**

Drug Safety & Toxicology Discussion Topics

- SSRIs as an example of drug safety policy dilemmas
- How do we review safety during development and marketing?
- Science, policy and values in risk/benefit assessment
- Q & A

SSRI Antidepressants

- Dramatic increased use in last decade
- Modest decrease in youth suicide risk
- Some studies link suicidality (NOT suicide) to use of drugs
- Press, professional associations, Congress in complex interplay

SSRI Brief Chronology

- 1991: FDA A.C. on suicidality and Prozac – no evidence for link
- 1997: Congressional incentives to conduct studies in children
- 2002: Paxil study submitted to agency. More analysis on s.
- 2003: Reanalysis submitted to FDA, FDA issues Public Health Advisory
- UK Contraindicates Paxil in pediatric depression (never approved in US)

SSRI Brief Chronology, continued

- 7/2003: FDA asks all sponsors to analyze pediatric clinical trials for s
- Fall 2003:FDA determines need for patient-level data to explore for confounding,
- A.C. - risks of over-warning without adequate support, second PHA urges caution and monitoring

SSRI Brief Chronology, continued

- 12/2003: UK contraindicates all SSRI in peds, FDA sends data to Columbia
- 3/2004: 3rd AC, FDA announces label requirement for Warning on monitoring
- 8/2004: Columbia data analysis completed, 4th AC mtg: no contraindication, all trial data should be public, Warning on all depression drugs, Med Guide, “black-box”
- 10/2004: FDA announces implementation of all AC recommendations
- American Psychiatric Association criticizes agency for overwarning

FDA Requirements for PreMarket Evaluation

- **Law & FD&C Act: "All tests reasonably applicable…" to safety**
- **Regulations: Information that "the product is safe….for recommended use"**
- **Guidance: safety database expectations under ICH**
- **Safety testing usually equals "patient exposure" to drug – trials explicitly evaluating drug safety are rare**

ICH Guidances: Safety Database

- **Chronically Administered Drugs**
  - **300 – 600 patients observed for 6 months**
  - **100 patients observed for 12 months**
  - **Total number of patients about 1500**
- **Extensive Caveats Related to Drug Class- e.g., NSAIDs**
- **Frequently, size of premarket safety database is determined by the efficacy trial needs**
- **Class-specific concerns create additional requirements for safety testing**

Detection of Side Effects Before Drug Approval

- **Common, pharmacologically-based, dose-related effects detected & qualified**
- **Infrequent (e.g., 1 in 300) effects often observed, rate unknown**
- **Rare or time-dependent effects often not known**
- **Increased frequency of event with appreciable background rate hard to detect**

Detection of Side Effects After Marketing

- Sponsor may agree to pursue specific safety studies post market. FDA cannot condition approval on performance of post market studies for safety
- Sponsor may conduct studies to gain as additional safety claim or efficacy claim

Detection of Side Effects After Marketing (cont.)

- **Spontaneous reporting system (MEDWATCH) useful for detecting rare side effects that are otherwise uncommon in the population**

- **FDA cannot require additional safety studies subsequent to approval. FDA can only move to take drug off the market**

Why Isn't Current Drug Development more Informative About Safety?

- **Primary goal of development programs has been demonstrating efficacy**
- **Traditional safety evaluation – animal toxicology plus observation – changed little over many decades**
- **No national program to evaluate longer term outcomes of drug therapy**
- **No national pharmacovigilance system**

Opportunities to Improve Safety Evaluation in Drug Development

- **New methods- toxicogenomics/pharmacogenomics**
- **Quantitative disease modeling & trial simulation**
- **Imaging as a biomarker**
- **Innovative trial designs**

Drug Safety Policy Issues

- International harmonization
- Access to clinical trial data, particularly on negative studies
- FDA role regarding safety “signals”
- Introduction of new products – balance of risk and benefits
- How to effectively communicate about products to medical community

Summary

- Severe issues in the pipeline of innovative new medical products
- Recent safety issues have complex causes
- Solutions involve difficult policy choices
- Informed debate requires participation of range of stakeholders
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